Exercise capacity, arterial oxygen saturation, hemoglobin concentration, and physical activity

A cross-sectional study of selected factors associated with the adaptation to high altitude, a comparison of 9-10 year old native Tibetan and Chinese immigrants in Lhasa, Tibet

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TERMINOLOGY AND ABBREVIATIONS

Adaptation – refers to a feature of structure, function, or behavior that enables an organism to live and reproduce in a given environment (1).

Acclimatization – refers to the time-dependent physiological responses that occur following exposure to high altitude (1).

Alveolar-arterial oxygen difference [(A-a)DO_2] - the difference in oxygen pressure between the alveoli (A) and the arterial blood (a). This can vary as the result of changes in either of these variables, matching of pulmonary blood flow to the ventilated regions of the lung, membrane surface area, and/or diffusing capacity (1).

Arterial oxygen saturation (SaO_2) - the percent of the heme (the deep red, non-protein, ferrous component of hemoglobin) groups in the hemoglobin molecule in the blood which are bound with oxygen (1). In the present study it is measured with a pulse oximeter as SpO_2.

Cardiac output - the volume of blood pumped by the heart per minute. It is the product of heart rate (beats/minute) and stroke volume (milliliters/beat). Stroke volume, in turn, is regulated by pre-load (right and left heart filling pressures), myocardial contractility (the percent of the ventricular volume expelled/beat), and after load (pulmonary and systemic blood pressure or vascular resistance) (1).

Cor pulmonale - Failure of the right side of the heart caused by prolonged high blood pressure in the pulmonary artery (called pulmonary hypertension) and right ventricle of the heart (5).

Exercise capacity ($\dot{V}O_{2\,max}$) – The maximal work performance or amount of O_2 that can be consumed by the tissues. It is conventionally measured as the level of O_2 consumption at which an increase in work load and it is expressed as milliliters of oxygen per kilogram of body weight per minute. It will be measured indirectly from the maximal watt cycle ergometer (MWCE) test, which is a standard bicycle test. Aerobic capacity, aerobic power, functional capacity, functional aerobic capacity, maximal functional capacity, cardio-respiratory fitness, cardiovascular fitness are terms that are often used interchangeably (1).

Hemoglobin concentration ([Hb])- the amount of hemoglobin in the blood, usually expressed in *g/dl*. It is comprised of hemoglobin able to bind or release oxygen (oxyhemoglobin, deoxyhemoglobin) as well as hemoglobin bound to other substances or unable to bind oxygen (carboxyhemoglobin, methemoglobin) (1).

Hemoglobin-oxygen affinity - the extent to which oxygen is tightly bound to hemoglobin. This varies depending on the amount of oxygen present and the temperature, the pH, and the presence of other compounds in the blood. It is measured as the position of the hemoglobin-oxygen dissociation curve, often indexed as the P50 or the oxygen pressure at which hemoglobin is half-saturated with oxygen (1).

Hypoxemia – Reduced oxygen delivery to the tissues as the result of lower blood oxygen content or reduced tissue blood flow (1).

Physical activity – is bodily movement produced by skeletal muscle contraction resulting in a substantial increase in energy expenditure. Physical activity has both an occupational and leisure basis that includes both active recreation pursuits like golf, tennis, and swimming. It also includes other active pastimes like gardening, cutting wood, and carpentry. Physical activity can provide progressive health benefits and be a catalyst for improving health attitudes, health habits, and lifestyle (2).

Polycythemia - a condition in which there are too many red blood cells (hemoglobin) in the blood circulation. It is the opposite of anemia, which results from too few red blood cells in the blood circulation. It is also called erythrocytosis (3).

Pulmonary hypertension - a rare lung disorder characterized by increased pressure in the pulmonary artery. The pulmonary artery carries oxygen-poor blood from the lower chamber on the right side of the heart (right ventricle) to the lungs where it picks up oxygen (4).

Ventilation - the amount of air breathed out per minute under resting conditions. It is also called minute or resting ventilation and is expressed in liters BTPS (body temperature pressure saturated) /minute. It includes air moving through the alveoli (areas of gas exchange) and dead space (bronchi, trachea), referred to as alveolar ventilation and dead space ventilation (1).

Processus xiphoideus - tip of the sternum

VO_2 - oxygen uptake or oxygen consumption

$ml\cdot kg^{-1}\cdot min^{-1}$ - milliliter per kilogram body weight per minute

rpm - revolutions per minute

W – watt

Wpeak – maximal workload

Wpeak/kg – body weight related maximal workload

P_{IO2} – inspired oxygen partial pressure

m – meter

hPa – hectopascal

mmHg – millimeters of mercury

BMI - Body mass index

TAR – Tibet Autonomous Region

ABSTRACT

Aim**:** It is well known that capacity for exercise performance is progressively limited with increasing altitude. Furthermore, the maximal exercise capacity is an indicator of the capacity of humans to adapt and acclimatize to high altitude. Chronic Mountain Sickness (CMS) is associated with inadequate adaptation or acclimatization abilities to high altitude. CMS is more common among immigrants who have immigrated from areas of low altitude to high altitude areas than among native highlanders. Any differences in factors related to the acclimatization ability between populations living in high altitude may indicate differences in risk of CMS. In Tibet, the prevalence of CMS among natives Tibetans older than 15 years is estimated to 1.2% and among immigrants from low altitude inland areas of China the prevalence is 5.6%. The aim of the present study is to investigate possible differences between native Tibetan children and immigrant children with respect to selected factors which may be potential risk factors for later development of CMS, such as peak workload (W_{peak}), hemoglobin concentration ([Hb]), arterial oxygen saturation (SpO_2), and physical activity levels.

Methods: The present cross-sectional study was carried out among 9-10 year old Tibetan (n=406) and Chinese (n=406) children in Lhasa, Tibet. Nine primary schools were randomly chosen and the subjects were considered representative for children living at the altitude of 3,700m above sea level. Peak workload, arterial oxygen saturation and heart rate were measured at rest and during Maximal Watt Cycle Eegometer (MWCE) test. Furthermore, hemoglobin concentration was measured and anthropometric measurements were recorded. Finally, a questionnaire about physical activity, food habits (PEACH-questionnaire and WHO questions) and socio-demographic factors was included.

Results**:** Both Tibetan boys and girls reached significant higher W_{peak} compared with Chinese (boys: 107.3 ±1.0 vs. 96.7 ±1.0 W, p<0.001; girls: 93.8 ±1.2 vs. 87.9 ±1.1 W, p<0.001). Only Tibetan boys had higher weight related relative W_{peak} than Chinese (3.7 ±0.03 vs. 3.5 ±0.03 W, p=0.002). Both Tibetan boys (197.6 ±0.7 vs. 194.4 ±0.6 beat/min, p<0.001) and girls (197.5 ±0.6 vs. 194.8 ±0.7 beat/min, p=0.005) had higher

heart rate at maximal exercise than Chinese but there was no difference in heart rate at rest. SpO_2 at rest was higher in Tibetan than Chinese and the difference was significant for girls only (91.1 ±0.2 vs. 90.2 ±0.3%, p=0.004). SpO_2 at maximal exercise was significant higher in Tibetan boys and girls than Chinese (boys: 87.3 ±0.3 vs. 84.7 ±0.3%, p<0.001; girls: 87.9 ±0.3 vs. 85.1 ±0.4%, p<0.001), while [Hb] was lower in Tibetan than Chinese children (boys: 14.6 ±0.1 vs. 15.3 ±0.1g/dL; girls: 14.6 ±0.1 vs. 15.4 ±0.1g/dL, p<0.001). Moreover, Both Chinese boys and girls as compared with Tibetans look less physical activities in the school areas after the school day was finished (boys: p=0.002; girls: p=0.018) and the Chinese boys were less physically active with respect to outdoor activities outside school (p=0.030).

Conclusion: Higher W_{peak} and SpO_2 at maximal exercise indicate that Tibetan children have higher exercise capacity than Chinese. The lower exercise capacity together with higher [Hb] among Chinese children may indicate that Chinese children are at greater risk for developing CMS later in life. However, the hypothesis should be verified in a prospective study.

CHAPTER I

BACKGROUND AND INTRODUCTION

I BACKGROUND AND INTRODUCTION

1 Background

Most of the population in Tibet live at altitudes higher than 3,500 meters above sea level. Among this population of native Tibetan highlanders, Chronic Mountain Sickness (CMS) occur, and the prevalence is estimated to be 1.2% in the population older than 15 yeas (6). During the last few decades there has been an increasing immigration of Chinese from inland China, from areas close to sea level. The prevalence of CMS among immigrants is estimated to be 5.6% (6). It is likely that the difference in CMS prevalence between native Tibetans and immigrants is due to differences in some factors related to the ability to acclimatize to high altitude (7). The immigration to Tibet will probably increase during the coming years due to the newly opened railway which connects inland China with Tibet. And thus, the number of CMS cases will increase in Tibet. According to the statistics of the 2005 Tibet Population Sampling Survey the resident population in Tibet amounts to 2.76 million (8), and the Chinese population is 6.5% (9) of the total population. It is estimated that about 2,500,000 tourists will visit Tibet every year after the opening of the railway, which will also increase the problem with acute mountain sickness (AMS) in Tibet. The present thesis focuses on the research question: what are the differences between native Tibetan children and immigrant Chinese children living at 3,700 m above sea level (Lhasa, Tibet) in selected factors related to the acclimatization process and the adaptation to high altitude? The main factors to be compared in the present thesis are: peak workload, hemoglobin concentration and arterial oxygen saturation during maximal exercise and rest. In addition, we have collected data on lung function. However, lung function data is not presented in the thesis, but will be an important part of the PhD work, together with the data from this thesis. The PhD- work will begin in January 2007. The present cross-sectional study may contribute to the research on the causes and mechanism for development of CMS.

2 Introduction

2.1 Definition of High altitude

Moderate altitude is defined as 1,500-3,500 m above sea level, high altitude as 3,500-5,500 m above sea level, and extreme altitude as 5,500-8,848 m or more above sea level (10). The three major high-altitude regions in the world are the Himalayas of Asia, the Andes of South America and the Rocky Mountains of North America.

The Himalayan (Qinghai-Tibetan) Plateau is the largest of these high altitude regions. It is roughly oval in shape, stretching 2,400 km east to west and 1100 km along its north-south axis and encompassing over 2,072,000 km^2 (for more details see appendix ı); The Andean Altiplano extends nearly 4,800 km along nearly the whole of South America, averaging 200 km wide and encompassing nearly 1,036,000 km^2; The Rocky Mountain Plateau encompasses an oval region, approximately 1200 km long and 400 km wide or nearly 388,500 km^2 (11). Among these three regions, people have lived for the longest time (about 50,000 years) in the Tibetan plateau, for an intermediate duration of time (about 9,000-12,000 years) in the Andean altiplano, and for the shortest duration of time (not inhabited permanently until about 150years ago) in the Rocky Mountain region (1).

Map of Tibet (12)

2.2 Definition of chronic mountain sickness (CMS)

CMS or Monge's disease has been described as an excessive erythrocytosis due to hypoventilation. It is a syndrome which may be caused by reduced ability of adaptation to live at high altitude, which may occur in indigenous or long-term residents at high altitude above 3,000 meters. High altitude polycythemia is also a synonym of CMS. The susceptibility to CMS appears to be greater among migrants than natives (1;6). The Chinese diagnostic criteria of CMS, which is internationally accepted, are as follows (6):

Based on scores from ten symptoms and signs, hemoglobin concentration ([Hb]), and arterial oxygen saturation (SpO_2), CMS might be defined as mild (score 6-10), moderate (score 11-14), and severe (score ≥15).

- The ten symptoms and signs used for scoring CMS are headache, dizziness, loss of memory, fatigue, breathlessness/or palpitations sleep disturbances, tinnitus, anorexia, cyanosis of lips, face or fingers, and hyperemia and prominent capillaries of conjunctive or laryngopharynx. Each symptom and sign is scored as 1, 2 and 3 for mild, moderate and severe appearance, respectively.
- [Hb] and SpO_2:

	[Hb] (g/dL)	S_pO_2 (%)	score
Male	18-21		0 (negative)
	≥ 21		3
		≤ 85	3
Female	16-19		0 (negative)
	≥ 19		3
		≤ 85	3

- Patients with severe headache, [Hb] ≥ 25.0g/dl, and SpO_2 ≤ 80% with overall score ≥ 15 indicate severe CMS and should immediately move down to lower altitudes.

2.3 Prevalence of CMS

A study by Moore et al. (1) showed that the prevalence of CMS is greatest in Han migrants as compared with native Tibetans. They reported that the prevalence is intermediate in lifelong Andean residents, and lowest in Tibetan highlanders. However, prevalence information is almost not available for the Rocky Mountain region. Moore et al. (1) summarized the date from different studies as shown in Table1 and 2.

Table 1. CMS prevalence (%) in immigrant Chinese and native Tibetan living in Tibet and Peruvians living in the Andes by altitude and gender

	Males			Females		
Altitude(m)	Han	Peruvians	Tibetans	Han	Peruvians	Tibetans
2260-2800	1.4	–	0.0	0.7	–	0.0
3050-3800	9.1	–	0.8	1.6	–	0.3
4000-5200	9.8	15.6	3.0	6.0	8.8	1.6

Table 2. Prevalence (%) of excessive polycythemia[1] in the Tibet Autonomous Region in 3,201 male (n= 1,749) and female (n=1,452) migrants (Han) and native highlanders (Tibetans) older than 15 years (Xie and Pei, 1981)

	Males			Females		
Region (altitude)	Migrants (workers)	Natives (workers)	Natives (farmers,herders)	Migrants (workers)	Natives (workers)	Natives (farmers,herders)
Lhasa (3,658m)	12.97	1.05	0	1.64	0	0
Gyangze(4,040m)	31.5	4.8	1.5	3.8	0	0.3
Nagchu (4,500-4,700m)	38.4	14.4	6.6	7.2	6.5	2.7

[1] Excessive polycythemia at 3,658 and 4,040 m was defined as red blood cell (RBC) counts>6.5 × 10^6/ul blood and hemoglobin (hgb) >20 g/dl blood, RBC counts >7.15 × 10^6/ul, or hgb >22 g/dl. At 4,500–4,700 m, excessive polycythemia was considered as RBC>7.0×10^6/ul and hgb>21 g/dl, or RBC >7.7×10^6/ul, or hgb>23 g/dl.

2.4 Mechanisms of developing CMS

Sime et al (13) have postulated the sequence of hypoventilation, hypoxemia, excessive erythrocytosis, and CMS as a causal pathophysiologic relationship. The partial pressure of oxygen is decreased at high altitude, which induces a decrease in the absolute rate of oxygen available per unit of pulmonary surface and a reduction in the saturation of oxygen in the blood (14). Lack of oxygen can result in Hypoxemia and consequently, the hypoxemia-induced polycythemia increases whole blood viscosity and thus resistances to blood flow through the lungs. Together with the increased cardiac output, the increased resistance may lead to pulmonary hypertension, causing cor pulmonale (right-heart failure). Polycythemia is a well-recognized adaptation to high altitude that sometimes becomes excessive, leading to CMS. Severe polycythemia impairs the distribution of pulmonary blood flow and pulmonary ventilation-perfusion relationships (decreasing V_A/Q). Impaired pulmonary gas exchange further augments the degree of arterial hypoxemia, which stimulates further hematopoiesis in a positive feedback loop, resulting in a higher rise in hemoglobin concentration. This is a vicious cycle for people with CMS (15). Patients with CMS present higher end-tidal carbon dioxide tension and lower end-tidal oxygen tension comparing with healthy high-altitude residents, suggesting an HVR (hypoxic ventilatory response)-independent lower level of alveolar ventilation in these subjects (16).

2.5 CMS associated factors

Altitude

The prevalence of CMS increases progressively as altitude increases. It is reported (6) that the prevalence of CMS is 1.1% at 2,980 m, 3.8% at 3,128 to 3,980 m, and 11.8% at 4,006 to 5,226 m above sea level in Chinese immigrants. It also showed that CMS is uncommon on the altitude below 3,000m above see level. Chao et al (17) found the prevalence of CMS in young soldiers who had relatively short time (9-21 months) at 5,000 m to be 30.43% compared with 9.33% in the Chinese troops in Lhasa (at 3,700 m).

Hemoglobin concentration and arterial oxygen saturation

The normal values of [Hb] and SpO_2 at sea level may not be adequate for use at high altitude. The value for Qinghai-Tibet is shown in Table 3. Before puberty, [Hb] in Tibetan boys and girls are similar to values in Chinese children. It is also reported (18) the hemoglobin values among 1 - 15 years olds in South Peruvian Andes at three different altitudes are shown in Table 4 (18). In addition, studies (19-22) comparing arterial oxygen saturation at rest and maximal exercise between native Tibetan and immigrated Chinese are shown in Table 5. One study (23) established the reference value for SpO_2 in healthy school children and adolescents living at 4,100 m in the south Peruvian Andes. In Table 6, the arterial oxygen saturation values in three different groups from the Peruvian Andes are shown, indicating quite similar values. Reeves et al. (15) suggested that [Hb] of 17.5g/dl and a SpO_2 of approximately 87% to be at the upper limit for effective oxygen transport in adult altitude residents.

Table 3. Normal Hemoglobin values (mean ± SD)for Tibetan and Chinese male and female residents of the Tibetan Plateau by altitude and age groups between 5 and 60 years (24).

Altitude	Males			Females		
	5–15 yr	16–40 yr	41–60 yr	5–15 yr	16–40 yr	41–60 yr
			Tibetan			
2,664	13.4±0.9	14.4±1.5*	14.7±1.6	13.4±1.0	12.8±1.5	13.0±1.6
n	42	215	171	58	150	176
3,813	14.3±1.0	15.3±1.7*	15.5±1.7	14.0±1.1	14.1±1.4	14.4±1.1
n	66	262	241	44	236	206
4,525	14.6±0.9	15.6±1.5*	15.7±1.6	14.4±1.0	14.5±1.7	14.7±1.5
n	68	288	231	32	228	204
5,200	14.6±0.8	15.7±0.8*	15.7±0.8	14.5±0.8	14.6±0.8	14.7±0.8
n	12	15	15	10	15	15
			Chinese			
2,664	13.7±0.9	15.6±1.7*	15.6±2.0	13.7±0.9	14.0±1.7	14.5±1.5*
n	72	348	282	54	174	161
3,813	15.3±1.2	18.1±1.6*	18.4±1.4	14.8±1.1	15.1±1.8	15.5±1.6
n	54	323	283	38	185	174
4,525	16.1±1.2	18.6±1.7*	19.0±1.6*	15.4±1.2	16.1±1.6	16.8±1.8*
n	28	208	187	18	145	82
5,200	17.1±1.2	19.6±1.6*	19.6±1.5	15.6±1.1	16.3±1.4	16.9±1.4
n	6	15	15	5	15	15

Values are means in g/dl ± SD. Values are shown for three altitudes (in m) and three age ranges (in yr). Number of subjects is indicated (*n*). * Within an ethnic, gender, and altitude group, the hemoglobin concentration was higher ($P < 0.05$) in the 16- to 40- than in the 5- to 15-year-old age group or in the 41- to 60- than in the 16- to 40-year-old age group.

Table 4. Hemoglobin value among 1 to 15 year old in South Peruvian Andes at three different altitudes (18).

	Boys			Girls		
altitude	4355	4660	5500	4355	4660	5500
[Hb] (g/dl)	16.11	17.10	17.60	15.63	16.62	17.55

Table 5. Comparison of arterial oxygen saturation at rest (SpO_{2rest}) and maximal exercise (SpO_{2peak}) between native Tibetan and immigrated Chinese by age and altitude.

Ethnicity	Altitude (m)	Age	Number	W_{peak} (w)	SpO_{2rest} (%)	SpO_{2peak} (%)
Tibetan	3,658 (19)	20-30 yr	16	177±5	90.5±0.5	83.7±1.5
	4,700 (20)	24-46 yr	17	167.7±4.2		
	3,658 (22)	20-30 yr	10	203±8	88±0	86±1
	3,417 (21)	13-16 yr	26	123.5±4.7	89.7±0.9	85.0±0.8
	4,300 (21)	13-16 yr	21	116.9±4.3	88.5±0.8	82.2±1.0
Chinese	3,658 (19)	20-30 yr	20	155±6	90.6±0.5	83.9±0.9
	4,700 (20)	24-46 yr	14	150.0±5.9		
	3,658 (22)	20-30 yr	9	195±9	89±0	82±1
	3,417 (21)	13-16 yr	28	112.5±3.8	89.2±1.1	80.5±1.2
	4,300 (21)	13-16 yr	14	92.9±5.1	87.2±1.1	72.1±2.1

Table 6. Mean (SD) values of SpO_2 (%) among school children and adolescence living at 4,100 m in the south Peruvian Andes by ethniciry.

Ethnicity	n	SpO_2 (%)
Quechua*	524	90.1 (3.1)
Quechun-Mestizo	428	90.4 (2.7)
Spanish-Mestizo	184	89.8 (2.6)

* Quechua is the native resident in Andes

Hypoxic ventilatory response (HVR)

It has been demonstrated that increasing duration of high-altitude residence is correlated with decreasing HVR (25). Observations from one study (26) have demonstrated that rest ventilation declines from age 11 (the youngest age measured) until about age 20, afterward remains unchanged in both lowlanders and highlanders. Curran LS et al. (27) found that increasing age was associated with a decline in ventilatory response among Tibetans living at 4,400m. HVR may therefore be a risk factor for development of CMS. A greater HVR may indicate a better exercise capacity at high altitudes (28). At higher altitudes, the in-equal ventilation may worse hypoxemia with increasing workloads (29). It has been showed that CMS patients have impaired ventilation and gas-exchange compared to healthy sojourners and, by implication to healthy Tibetans (30). Sun et al (31) showed that patients with CMS exhibited hypoventilation, lower tidal volume, blunted HVR, and a depressant effect of ambient hypoxia on ventilation compared with control subjects in Lhasa. Based on the above physiological observations CMS patients will present poorer exercise capacity.

Gender

CMS occurs more often in men than in women, especially at moderate altitudes. The ten years' study in Qinghai-Tibet among the population above the age of 15 shows the prevalence of CMS in Chinese women of 1.8% as compared with 7.8% in Chinese men at 4300 m. The prevalence in Tibetan women and men is 0.6% and 1.8%, respectively (6). High hemoglobin concentration in men may be due to hormone differences. It has been shown (32) that testosterone is the stimulator of erythropoiesis and erythropoietin (EPO) production. It has also been shown (30) that excessive polycythemia is more common among male Chinese sojourners than among male Tibetans. Therefore, Chinese men may have a greater erythropoietic response to a given testosterone concentration than do Tibetan men. Besides, genetic differences in ventilatory responsiveness to hypoxia between Han and Tibetan populations may exist, and testosterone may have a greater ventilatory depressant effect in Han than in Tibetan men.

Age

Studies in Peru suggested that age is a main causative factor for CMS because of an age-dependent polycythemia is based on an age-dependent loss of ventilation and arterial hypoxemia (6). Hemoglobin concentrations increase with age in both sexes, which is confirmed in previous observations (13;33;34). Gender-related differences in hemoglobin can only be seen after puberty (18). Moreover, menopause is a risk factor for the development of excessive erythrocytosis (35). It has been confirmed (18) among native Andean woman living at 4355 and 4660 m that hemoglobin are higher in the older age groups (40-60yr) than in the younger age groups (16-40yr and 1-15yr).

Ethnicity

CMS is more common in Chinese than native Tibetans (6;36) indicating an association between ethnicity and CMS. Native Tibetans are probably at less at risk of CMS than indigenous Andeans, as well (36-40).

Length of residence

The development of CMS usually requires years of residence at high altitude, but Chinese immigrants may develop CMS after shorter residence than native Tibetans in Tibet (6). It is also been reported that Chinese young soldiers may develop CMS after a short duration of stay of 9-21months at 5,000m (17).

Occupation

According to Wu (6), the prevalence of CMS is higher among Professionals than farmers and nomads. Furthermore, high-altitude inhabitants will be at higher risk of developing CMS if the regions become more urbanized or industrialized.

2.6 Exercise capacity and physical activity in relation with CMS

$\dot{V}O_{2\,max}$ is widely recognized as the best single measure of maximal exercise capacity. The maximal exercise capacity may indicate the capacity of humans to acclimatize to high altitude, as well as an indicator of adaptation among highlanders. If this is correct, $\dot{V}O_{2\,max}$ may be a predictor for CMS. We are not aware of longitudinal studies where highlanders with different $\dot{V}O_{2\,max}$ are followed for long time until development of CMS.

Studies from Tibet (19-22) show that adult and adolescent Tibetans achieved greater exercise capacity than Chinese (Table 5). It has also been demonstrated that exercise capacity in children at high altitude is influenced by developmental factors in concert with nutrition, levels of habitual activity, and socio-economic and environmental characteristics (41).

Some studies of the nutritional and health status of Tibetan children have previously been conducted (42-44) showing that poor nutrition status and growth retardation at high altitude.

Studies of $\dot{V}O_{2\,max}$ relation to physical activity in European countries (45-47) show that children who are more physically active may have higher $\dot{V}O_{2\,max}$ than others. As far as we know, there is no study regarding physical activity levels in Tibetan children.

3 Aim and research objectives

The ***aim*** of the present study is to investigate possible differences between native Tibetan children and immigrant children with respect to selected factors, which may be potential risk factors for later development of CMS, such as peak workload, hemoglobin concentration, and arterial oxygen saturation. The following are the detailed ***objectives*** for the study among 9-10 year old Tibetan and Han children in Lhasa, Tibet:

1. to compare the peak workload between the two groups
2. to compare hemoglobin concentration between the two groups
3. to compare arterial oxygen saturation during maximal exercise and rest between the two groups
4. to compare level of physical activity between the two groups

CHAPTER II

POPULATION AND METHODS

II POPULATION AND METHODS

1 Study design

The prsent study is cross-sectional. It is appropriate for the purpose of comparing native Tibetan children and immigrant children with respect to selected factors, such as peak workload, hemoglobin concentration, arterial oxygen saturation and level of physical activity.

2 Study population

2.1 Sample size

In the present study we compared Tibetan and Chinese girls and boys with respect to selected parameters. In order to estimate the needed size of our study-population, we used data from a similar study of Tanzanian and Norwegian children by Aandstad et al. (45). In that study, the standard deviation for peak workload ranged form 13.2 to 19.6 W. The standard deviation was 15.9 among 184 Norwegian girls aged 9 to 10 years old, which we used in the sample size calculation. The subjects needed in each of the groups to be compared in our study can be calculated according to the formula:

$n=2k\sigma^2/\Delta^2$

The multiplying factor k can be calculated based on α and β values. If $\alpha=0.05$ and $\beta=0.20$, the $k=7.8$. σ is the standard deviation and Δ is the expected differences in mean between groups to be compared. In this study we are interested in detecting differences in W_{peak} of 5 watt as statistical significant, i.e. $\Delta=5$. After putting figures into the formula, the sample size is estimated to be 159 in each group. We will do separate analysis for boys and girls and compare native Tibetan and Chinese immigrant children. Therefore we aimed at including 200 Tibetan girls and 200 Tibetan boys, and the same numbers for the Chinese, i.e. 800 participants.

2.2 Population

The children included in this study were 9 to 10 years old, born between 1st of January and 31st of December in 1995. From the list of schools in Lhasa we drew randomly 5 schools in the beginning. One teacher from each of the schools prepared a list of all 9 to 10 year-old students. All these students in the list were invited to participate in the study. The research team spent 4 to 10 days at each school. Less than 5 students were unable to participate, only one because of refusal. From these 5 schools we recruited 402 Tibetan (207 boys and 199 girls) and 228 Chinese (134 boys and 94 girls) students. According to the power calculation, we had to increase the number of Chinese students. Therefore, we randomly selected 4 more schools using the same procedure to recruit 178 more Chinese students (101 boys and 77 girls). In addition, 4 more Tibetans were included. Thus, the final sample consisted of 812 schoolchildren (406 Tibetan and 406 Han children) aged 9 to 10 years.

The 5 first selected schools and 3 of the last four selected schools were governmental (see appendix I).

3 Data collection

The data collection was done indoors in a separate room in each school without disturbing elements during 55 days from August to November of 2006, uninterruptedly. Pupils were tested one by one. There was no hard physical activity the day before the test. No food was consumed less than two hours and no big meals less than four hours previous to the bicycle test.

The data collection started at 09:30 on fifth of August in 2005 and about 15 children were tested each day. Three stations were arranged for the test. First station was for physical examination, where height, seat height, weight, chest circumference, belly circumference and hemoglobin concentration were measured; the second station was settled for MWCE test; and in the last station children filled in the questionnaire under supervision of a researcher.

Pilot

The pre-test served the purpose of identifying potential problems in the proposed study and examined the logic of the testing procedure and applicability. The pre-test was conducted with the whole research team in one school not selected for the main study.

The pre-test of questionnaire measured how much time was needed to complete each questionnaire; reveal unanticipated problems with question wording, instructions to skip questions, etc. It helped to see if children could understand questions and then give valid answers. Moreover, this process was important to ascertain the suitability of the questions in local cultural settings and to minimize the possibility of evoking undue responses or asking question that may have a different meaning to the local population. We discussed with all members of the team after pre-testing to ensure that the true meanings of questions were not lost during the process.

After pre-testing we revised the physical exam forms to make them easy to use during the exam (the examiner can be able to follow the flow).

3.1 Anthropometrics

The weight of the children was measured to the nearest 0.1 kg (without shoes and wearing light clothes), using Electronic Bathroom Scale (OMRON, HN-281). Height was measured to the nearest 0.5 cm, applying a height and seat height apparatus (TZG, Shanghai, China). Body Mass Index (BMI) was calculated as weight (in kg) divided on height squared (in meters).

3.2 Maximal Watt Cycle Ergometer (MWCE) test

The present study applied the same methods, which were used in the European Youth Heart Study (48) conducted in different European countries and similar to a comparison study between Tanzanian and Norwegian schoolchildren (45).

Peak workload was measured using a graded maximal exercise test on an electronically braked cycle ergometer (Monark Ergomedic 839, Varberg, Sweden), according to a reported protocol (49).

The bicycle was electronically calibrated once every test day and mechanically calibrated after being moved between schools. The height of the seat was regulated so that the heel was flat when the leg was fully stretched. The children were asked to lie down for 2-3 minutes before the test and the resting heart rate (HR_{rest}) and resting arterial oxygen saturation ($SpO_{2\ rest}$) were recorded. The children started at a workload of 20 watts, if their body mass was less than 30 kg, with a rise in workload of 20 watts for each 3 minutes. If their body mass was greater than 30 kg, the children started at a workload of 25 watts, with a rise in workload of 25 watts for each 3 minutes. The children cycled with a pedaling rate of 70-80 rpm. The workload was increased until the child was no longer able to keep a pedaling frequency of at least 30 rpm or more. There were two criteria for determining if the maximal exercise capacity was reached: 1. Heart rate above 185 beats per minute. 2. A subjective judgment by the test-leader that the child could no longer continues, even after vocal encouragement. We stopped to encourage subjects when the child could no longer continue with pedaling rate above 30 rpm.

Calculation of peak workload

The peak workload (W_{peak}) was calculated as watts in the last fully completed workload (W_1), plus the increment in watts (W_i) of the last step, multiplied by the number of seconds completed of the last step (t_{ls}) and finally divided by 180 seconds:

W_{peak}: $W_1 + (W_i \cdot t_{ls} / 180)$

Relative peak workload was measured as: W_{peak}/ body weight

3.3 Hemoglobin concentration

The HemoCue Hb 201+ analyzer (Ängelholm, Sweden) was applied to measure the hemoglobin concentration. A blood drop was collected by a finger tick. We applied the microcuvette to a drop of capillary blood. After wiping of any excess blood from the sides of the cuvette, it was placed in the cuvette holder and inserted into the photometer, and the result was displayed automatically. We calibrated the analyzer each testing day using the HemoCue Hemoglobin Calibrator (12.0±0.2).

3.4 Arterial oxygen saturation

The *Nellcor* NPB-40 (California, USA) handheld pulse oximeter was used for measuring arterial oxygen saturation. OXI-P/I OxiBand was applied for children less than 40 kg and DURASENSOR DS-100A for children above 40 kg, respectively. We cleaned the surface of the sensor and subject's finger with 70% isopropyl alcohol. The sensor was attached around the index finger. Before the test children had to lie down for 2-3 minutes and then resting arterial oxygen saturation ($SpO_{2\ rest}$) was recorded. The arterial oxygen saturation was recorded every third minute during the bicycle test.

3.5 Heart Rate

Heart rate sensor (Polar Electro OY, Kempele, Finland) was attached above processus xiphoideus. The children were asked to lie down for 2-3 minutes before MWCE test and the resting heart rate (HR_{rest}) were recorded. Subsequently, the heart rates were registered within the last 10 seconds of the every three minutes workload periods of test. The peak heart rate (HR_{peak}) were recorded together with peak arterial oxygen saturation ($SpO_{2\ peak}$) when the children were not able to keep a pedaling frequency of at least 30 rpm or more.

3.6 Questionnaire

The questionnaire consisted of questions about physical activity (PEACH-questionnaire and WHO questions), diet and socioeconomic factors. The questionnaire was translated from English into Chinese and back-translated by another person to ensure accuracy. The students filled in the questionnaire under the supervision of a fieldworker.

4 Data management

The complete fullness of the questionnaires and the results of physical examination were checked every day after data collection in the field. The data was checked and edited for inconsistency and entered into a computer.

5 Data analysis

The data was analyzed using both standard parametric and non-parametric tests. Differences in height, weight, W_{peak}, HR, SpO_2 and hemoglobin concentration between two ethnic groups were tested using the independent samples t-test. Difference between mean value of SpO_{2rest} and SpO_{2peak} was tested applying paired samples t-test. Chi-square (χ^2) tests were used when comparing differences in physical activity patterns. Two way analysis of variance with tukey post hoc test was used to analyze W_{peak} in relation to physical activity. $p \leq 0.05$ was considered as statistically significant. SPSS 12.0 was applied to enter data and date processing.

In view of the fact that Tibetan children were drawn from the first 5 schools (except 4 children) and Chinese children were drawn from 9 schools due to limited number of Chinese children in first 5 schools, we did separate analysis of comparison of W_{peak} between Tibetan and Chinese children (See tables in Appendix Ⅳ).

6 Ethical considerations

The study followed the directions given in the Helsinki-declaration approved on the 52^{nd} General assembly in October 2000. Official permission to conduct this study was granted by the Ministry of Education of TAR. The researcher (Bianba) was in charge of carrying out the data collection and field work according to local standards and legislation. Three researcher assistants were trained and assisted through the data collection.

The subjects were recruited from children who could refuse to participate and withdraw from the study for any reason at any time without any consequences for themselves. All information about the subjects was handled confidentially. The names of the subjects were not registered, but an eight figured code was used. The first figure represented the school, figure two and three represented the class, and fourth represented the sex and five to eight represented the individual subjects.

CHAPTER III

RESULTS

III Results

A total of 812 nine to ten year old schoolchildren participated in the present study, half of them were native Tibetans and half were Chinese immigrants. Among the Tibetan children 207 (51%) were boys and 199 (49%) were girls, while among the Chinese 235 (58%) were boys and 171 (42%) were girls. For three Tibetan students and four Chinese students we lack anthropometric measures, and 23 Tibetan and 48 Chinese students we lack the MWCE test (Figure 1) and hemoglobin concentration test. Among the children who participated in the MWCE test, there are 57 Tibetan and 82 Chinese shorter than 130cm. These children had difficulties on touching the pedal even though they finished the test. To sum up, 790 (97%) children participated in all tests.

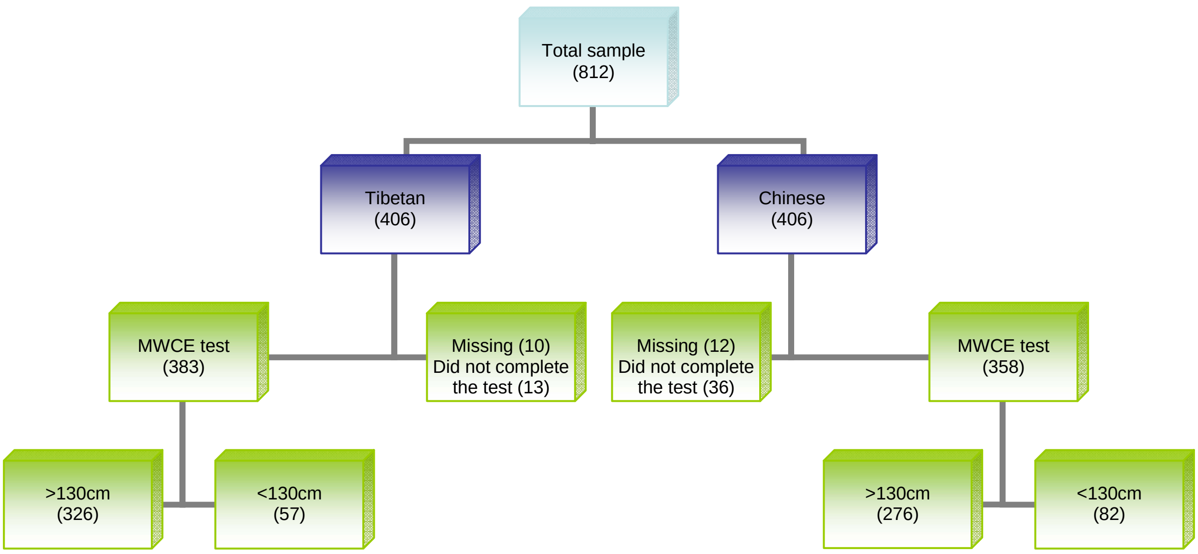

Figure 1. Flowchart of the number of 9-10 year old Tibetan and Chinese children failed or completed the MWCE test.

1 Background factors

1.1 Anthropometrics

Descriptive data of Tibetan and Chinese children are shown in Table 1a. Tibetan children were significantly heavier (boys: p<0.001; girls: p=0.001) and taller (boys: p=0.018; girls: p=0.002) than Chinese. Both Tibetan boys and girls had bigger chest circumferences (p<0.001) and belly circumferences (p<0.001) than Chinese. Both Tibetan boys and girls had higher BMI than Han Chinese boys (p<0.001) and girls (p=0.006).

Table 1a. Personal characteristics of total Tibetan and Chinese 9 to 10 year old schoolchildren

	Boys				Girls			
	Tibetan		Chinese		Tibetan		Chinese	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Weight (kg)	207	29.7 (29.0 - 30.4)	235	27.8 (27.1 - 28.4) **	198	29.4 (28.7 - 30.1)	169	27.6 (26.8 - 28.4) *
Height (cm)	207	134.8 (134.1 - 135.5)	234	133.5 (132.6 - 134.3) *	198	135.9 (134.9 - 136.8)	169	133.7 (132.7 - 134.7) *
BMI (kg/m^2)	207	16.1 (15.8 - 16.4)	234	15.4 (15.1 – 15.6) **	198	15.8 (15.6 – 16.1)	169	15.3 (14.9 – 15.6) *
Seat height (cm)	207	72.1 (71.7 - 72.6)	234	72.0 (71.6 - 72.4)	199	72.6 (72.1 - 73.0)	169	72.0 (71.5 - 72.5)
Chest (cm)	206	64.9 (64.3 - 65.6)	234	62.0 (61.5 - 62.6) **	198	63.9 (63.3 - 64.6)	169	61.5 (60.8 - 62.2) **
Belly (cm)	206	57.8 (57.0 - 58.7)	234	55.1 (54.4 - 55.8) **	198	56.2 (55.5 - 56.9)	169	53.7 (52.9 - 54.5) **

**p< 0.001,*p < 0.05 from the corresponding Tibetan value.

1.2 Physical activity patterns

There was significant difference in travelling pattern from home to school and back home again between Tibetan and Chinese children (Table 1b). A large proportion of children went on foot, both among girls (40.3% vs. 52.9%) and boys (39.5% vs. 54.1%) in Tibetan and Chinese, respectively. Both Chinese boys and girls were less active in taking part in exercise after school than Tibetans (boys: p=0.002; girls: p=0.018) and the Chinese boys were less active in playing games outside after school (p=0.030).

Table 1b. Physical activity patterns in Tibetan and Chinese 9 to 10 year old schoolchildren

	Boys					Girls				
	Tibetan		Chinese		p-value	Tibetan		Chinese		p-value
	n	%	n	%		n	%	n	%	
Means of transportation to school					<0.001					<0.001
Foot	81	39.5	126	54.1		79	40.3	90	52.9	
Bicycle	33	16.1	41	17.6		32	16.3	26	15.3	
Bus	41	20.0	45	19.3		37	18.9	40	23.5	
Car or motorcycle	50	24.4	21	9.0		48	24.5	14	8.2	
Total 5	205	100.0	233	100.0		196	100.0	170	100.0	
Means of transportation to home					<0.001					0.001
Foot	82	40.0	130	55.8		82	41.8	93	54.7	
Bicycle	34	16.6	42	18.0		32	16.3	26	15.3	
Bus	44	21.6	45	19.3		38	19.5	38	22.4	
Car or motorcycle	45	22.1	16	6.9		44	22.6	13	7.6	
Total 7	204	100.0	233	100.0		195	100.0	170	100.0	
Travelling time to school					0.002					0.001
<5min	65	31.7	51	22.1		65	33.3	38	22.5	
5-15min	97	47.3	118	51.1		101	51.8	75	44.4	
15-30min	31	15.1	58	25.1		24	12.3	43	25.4	
30-60min	9	4.4	4	1.7		3	1.5	11	6.5	
>1 hour	3	1.5	0	0		2	1.0	2	1.2	
Total 6	205	100.0	231	100.0		195	100.0	169	100.0	
Stay behind school to take part in exercise					0.002					0.018
Hardly ever or never	76	37.3	128	55.4		76	39.0	89	53.6	
1-2 times/week	82	40.2	64	27.7		87	44.6	49	29.5	
Most days	26	12.7	21	9.1		19	9.7	19	11.4	
Every day	20	9.8	18	7.8		13	6.7	9	5.4	
Total 7	204	100.0	231	100.0		195	100.0	166	100.0	
Play games outside after school					0.030					
Hardly ever or never	55	27.0	84	36.5		55	28.1	60	35.5	
1-2 times/week	70	34.3	82	35.7		80	40.8	68	40.2	
Most days	44	21.6	43	18.7		28	14.3	22	13.0	
Every day	35	17.2	21	9.1		33	16.8	19	11.2	
Total 6	204	100.0	230	100.0		196	100.0	169	100.0	

2 Hemoglobin concentration

The hemoglobin concentration was lower in both Tibetan boys ($p<0.001$) and girls ($p<0.001$) as compared with Chinese children (Figure 2, Table 2). In the Tibetans, the hemoglobin concentration at tenth percentile was about 13.0g/dl and hemoglobin concentration at ninetieth percentile was about 16.0g/dl; as compared with 13.8g/dl and 16.8g/dl respectively in Chinese children. Furthermore, there were no gender differences for both Tibetan and Chinese children (Figure 2, Table 2). Among the Chinese, the hemoglobin concentration was increased when the duration of stay in Lhasa was more than 4 years and the value decreased after 7 years staying in Lhasa (Table 2).

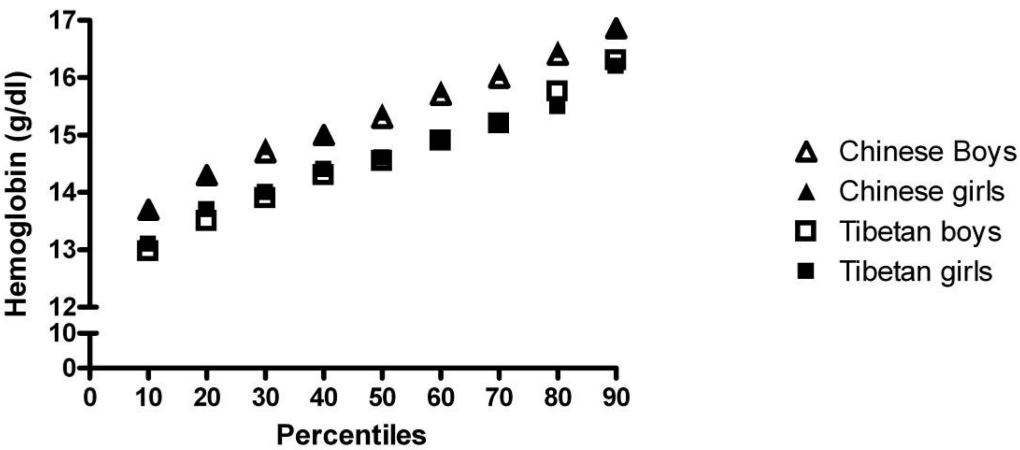

Figure 2. Hemoglobin concentration between 9-10 year old Tibetan and Chinese children by percentiles.

Table 2. Hemoglobin concentration (g/dl) in Tibetan and Chinese 9 to 10 year old schoolchildren.

	boys				Girls			
			95% CI				95% CI	
	n	mean	lower	upper	n	mean	lower	upper
Tibetan	206	14.6	14.4	14.8	199	14.7	14.5	14.8
Chinese	233	15.3	15.1	15.5	169	15.4	15.2	15.6

	Years of residence in Lhasa	n	mean	95% CI	
Chinese	≤3 yrs	144	15.3	15.1	15.5
	4-5 yrs	82	15.4	15.3	15.8
	6-7 yrs	51	15.5	15.1	15.8
	8-10 yrs	76	15.2	15.0	15.5

-

3 Maximal Watt Cycle Ergometer (MWCE) test

3.1 W_{peak} and weight related W_{peak}

Both Tibetan boys and girls had higher W_{peak} than Chinese children ($p<0.001$) (Figure 3). After excluding the children whose height was less than 130cm, which may indicate a problem with reaching the pedal properly, Tibetan children still had significant higher W_{peak} than Chinese (boys: $p<0.001$; girls: $p=0.001$). Tibetan boys and girls had higher weight related relative W_{peak} than Chinese (Figure 4), while the difference only reached statistically significant level among boys ($p=0.002$). Furthermore, the differences of relative W_{peak} between Tibetan and Chinese children were obvious among children who achieved lower workload (Figure 4). Table 3a shows mean values of W_{peak} in Tibetan and Chinese children, indicating a high W_{peak} among Tibetans.

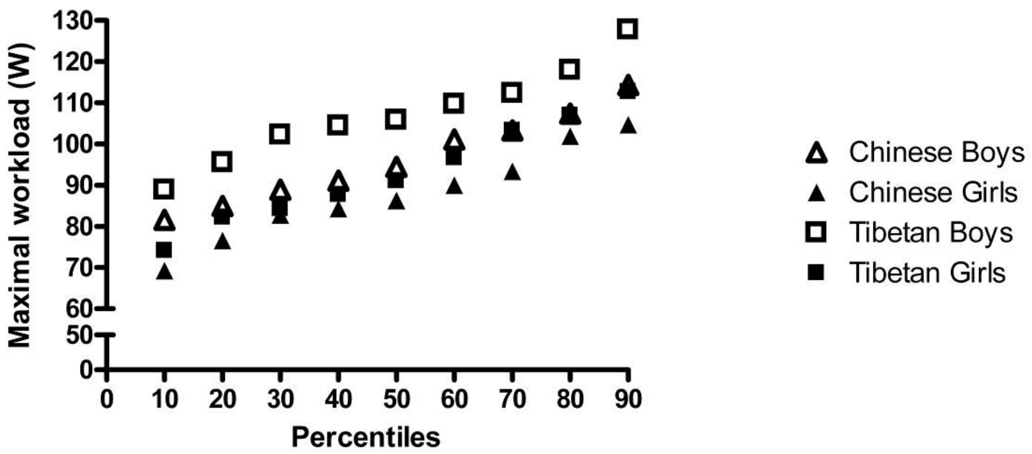

Figure 3. Wpeak in 9-10 year old Tibetan and Chinese children from MWCE test by percentiles.

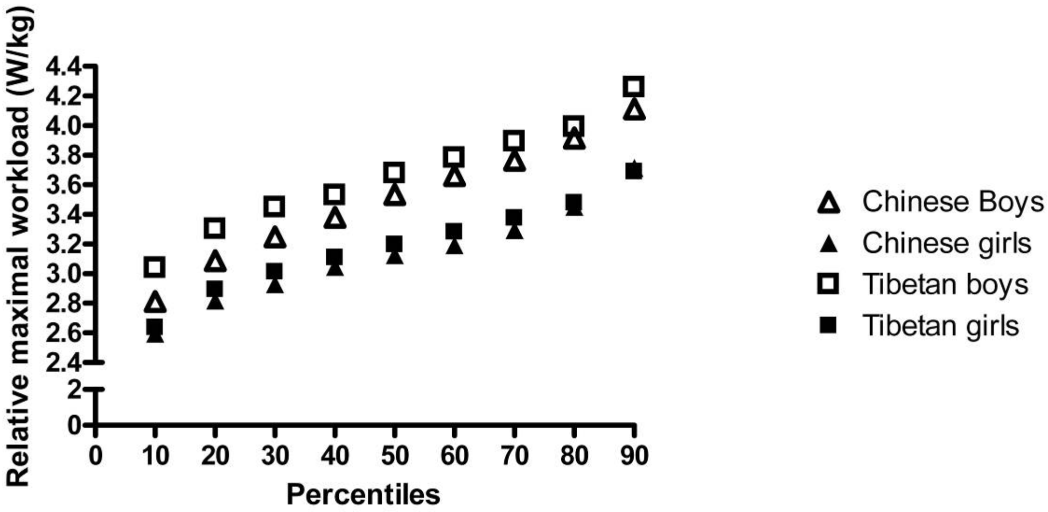

Figure 4. Weight related relative W_{peak} in 9-10 year old Tibetan and Chinese children from MWCE test by percentiles.

Table 3a. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test.

sex			N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	W_{peak}(w)	1-Tibetan	201	107,3	13,3	0,94	0.000
		2-Chinese	216	96,7	14,8	1,01	
	W_{peak}'	1-Tibetan	170	109,4	12,4	0,95	0.000
		2-Chinese	161	100,1	13,7	1,08	
2-Girl	W_{peak}(w)	1-Tibetan	182	93,8	16,1	1,20	0.000
		2-Chinese	142	87,9	13,0	1,09	
	W_{peak}'	1-Tibetan	154	96,2	15,1	1,22	0.001
		2-Chinese	113	90,5	12,1	1,14	

W_{peak}': after excluding those children whose height less than 130cm

3.1.1 W_{peak} and physical activity

W_{peak} was highest among the children who travel to school by bicycle and significantly higher among Tibetan bicycle riders than Chinese (Table 4).

Table 4. Mean W_{peak} of 9-10 year old Tibetan and Chinese children by method of travelling to school.

			N	Mean	SD	95% CI Lower Bound	95% CI Upper Bound
W_{peak}	Tibetan	by car or motorcycle	94	100.1	16.3	96.7	103.4
		by bus	73	98.8	16.7	94.9	102.7
		by bicycle	64	106.9	16.5	102.8	111.0
		by foot	149	100.0	15.4	97.5	102.5
	Chinese	by car or motorcycle	33	89.1	17.3	83.0	95.2
		by bus	78	91.2	13.7	88.1	94.3
		by bicycle	63	100.0	10.8	97.3	102.3
		by foot	183	92.4	15.3	90.2	94.7

3.1.2 W_{peak} and family income

Regarding to socioeconomic status, there was no significant relationship between family income and peak workload (data not shown). The majority of both Tibetan and Chinese children reported that they were quite rich (Table 5).

Table 5. Self-reported socioeconomic status among 9-10 year Tibetan and Chinese school children in Lhasa.

	Poor		Quiet rich		Very rich	
	N	%	N	%	N	%
Tibetan	17	4.3	346	86.9	35	8.8
Chinese	18	4.5	363	91.7	15	3.8
Total	35	4.4	709	89.3	50	6.3

3.2 Arterial oxygen saturation and heart rate

Both Tibetan boys and girls had significant higher SpO_2 at maximal exercise than Chinese, but the SpO_2 at rest was quite similar, but significantly higher among girls only than Chinese girls (p=0.004) (Table 7). The oxygen saturation decreased gradually with increasing cycle time for both Tibetan and Chinese children (Figure 5). Table 6 shows the number of Tibetan and Chinese who completed the bicycle test from rest to 15 minutes.

Table 6. The number of 9-10 year old Tibetan and Chinese schoolchildren at different cycle time during MWCE test.

	rest	3min	6min	9min	12min	15min
Tibetan	383	383	374	326	117	6
Chinese	358	355	351	277	81	5
Total	736	738	725	603	198	11

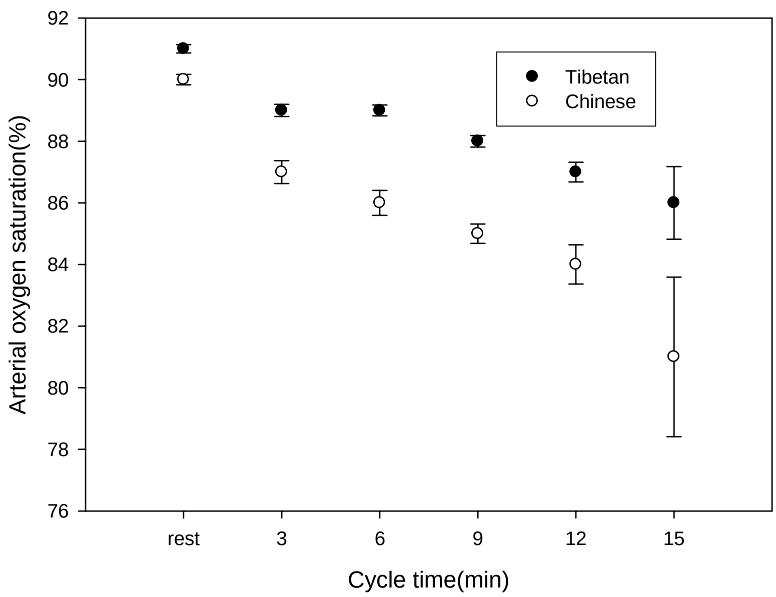

Figure 5. Alteration of arterial oxygen saturation from rest to maximal exercise from the MWCE test in 9-10 year old Tibetan and Chinese schoolchildren. Values are reported as means (95% CI).

Both Tibetan boys and girls had a significantly higher heart rate at maximal exercise but there was no difference at rest (Table 7).

Table 7. Heart rate at rest (HR_{rest}), finished heart rate (HR_{peak}), $SpO_{2\ rest}$ (arterial oxygen saturation at rest), SpO_{2peak} from the MWCE test and hemoglobin concentration level in Tibetan and Chinese 9 to 10 year old schoolchildren.

		boys				Girls			
				95% CI				95% CI	
		n	mean	lower	upper	n	mean	lower	upper
HR_{rest}	Tibetan	200	87	85.4	88.6	183	89	87.4	90.8
	Chinese	217	89	87.7	90.8	141	89	86.9	90.7
HR_{peak}	Tibetan	201	198	196.3	199.1	182	198	196.2	198.8
	Chinese	216	194	193.3	195.5	141	195	193.4	196.2
$SpO_{2\ rest}$	Tibetan	200	91	90.7	91.4	183	91	90.7	91.5
	Chinese	217	91	90.1	90.9	141	90	89.6	90.8
$SpO_{2\ peak}$	Tibetan	201	87	86.8	87.8	181	88	87.3	88.4
	Chinese	215	85	84.0	85.3	141	85	84.4	86.0

CHAPTER IV

DISCUSSION

IV Discussion

This study demonstrates that Tibetan 9-10 year old schoolchildren present higher peak workload and higher oxygen saturation at peak workload than Chinese. The body weight related W_{peak} reached only a statistically significant difference among boys. The study also revealed that Tibetan children had significant lower hemoglobin concentration compared to Chinese children. The study also showed that Tibetan boys and girls were more physically active than Chinese in leisure time.

1 Methodological discussion

The present study includes a large sample size, which ensures sufficient power to detect clinically meaningful differences between Tibetan and Chinese children with respect to the main variables. Thus, we were able to avoid to Type II error, we are able to detect a real difference as statistically significant. It is not likely that we have made a Type I error (i.e. detecting a significant difference between Tibetan and Chinese children when it is not true), because we have a limited number of tests for differences regarding our main variables.

Systematic error

In epidemiological observational studies there are always possibilities for systematic errors. The main problems to consider are: selection bias, information bias and confounding.

1.1 Selection bias

Selection bias is the error due to systematic differences in characteristics between those who are selected for study and those who are not. For example, subjects in a survey limited to volunteers or persons present in a particular place at a particular time (50).

Selection bias could thus be caused by a skewness in the children eligible for the study, but also skewness in the participation rate between Tibetan and Chinese children. It is not likely that there is a difference in school attendance between Tibetan and Chinese children with respect to the variables under study. But, it could be that more sick and disabled children do not attend the school as compared to healthy children. However, this will be similar for both Tibetan and Chinese. The present results are probably slightly better than if we had tested all 9-10 year old children (including those who did not attend the school), but the differences between Tibetan and Chinese would probably not have been affected. We have no exact data on school attendance in Tibet, but it is likely that more than 98% are enrolled in the school at the age of 9-10 years.

The response rate was high both among Tibetan and Chinese children indicating that the present result is not affected by a selection bias. However, in each of the schools, a teacher was responsible for making a list of all 9-10 year old children. We could not control if the lists were complete, but there is no reason to believe that the teachers have excluded children and less likely that a possible exclusion should be different in Tibetan as compared with Chinese children.

1.2 Information bias

Information bias is a flaw in measuring exposure or outcome data that results in different quality (accuracy) of information between comparison groups (50).

There could possibly be systematic difference between Tibetan and Chinese children in recording of exercise capacity, because the Tibetan research team could possibly encourage the Tibetans to work harder, and thus, perform better than Chinese. If this is a problem in the present study, it is not done by intension, and it is unlikely that it could change the results significantly. Tibetan children were drawn from 5 schools and the Chinese from the 5 and additional 4 schools in order to get a sufficient number of Chinese. Theoretically, there could be a difference between these schools in the factors of interest in the present study, i.e. children from the last 4 schools perform worse than children from the first 5 schools. However, when we compare separate W_{peak} between Chinese in all 9 schools, there are no significant differences (See Appendix IV).

The above mentioned problems could also fit for sex differences, i.e. boys or girls are encouraged to perform best in different manners. A systematic difference between Tibetan and Chinese in understanding the meaning of the questions in the questionnaire and in remembering facts which are asked for is unlikely.

1.3 Confounding and interaction

Confounding is a relationship between the effects of two or more causal factors as observed in a set of data such that it is not logically possible to separate the contribution that any single causal factor has made to an effect (50).

In the present study, we have presented mean values or proportions for sub-groups. We have not adjusted mean values for possible confounders, but we have done sub-group analysis, for example, W_{peak} by method of transportation to school and by social status. In order to avoid interaction problems, we have done separate analysis among boys and girls. However, a more detailed analysis of possible confounding and interaction will be done in the PhD-period starting in January, 2007.

2 Discussion of results

2.1 Peak workload

This study used the indirect measure W_{peak} to evaluate the children's exercise capacity. However, it has been shown (49) that W_{peak} can be used for calculating of $\dot{V}O_{2\,max}$, providing a valid indicator of the direct measurement of exercise capacity ($\dot{V}O_{2\,max}$).
The higher W_{peak} in Tibetan children in this study indicated that they have greater exercise capacity. This could be due to several factors including higher oxygen content of the blood, raising blood flow to the working muscle and other tissues, or higher amount of oxygen extracted by the tissues among the Tibetan compared with the Chinese:

Oxygen content of the blood is determined by ventilation, alveolar-arterial oxygen difference [(A-a) DO2], hemoglobin-oxygen affinity, and hemoglobin concentration. Hypoxic ventilatory response (HVR) is an important factor which influences ventilation at high altitude (51-54). It is revealed that adult Tibetan inhabitants have hypoxic ventilatory responsiveness (HVRs) higher than acclimatized new comers who have migrated to high altitude when they were children (25;55;56). The greater alveolar ventilation and higher HVR are likely to help Tibetans maintaining arterial oxygenation at rest as well as during exercise (1).

[(A-a) DO2] and hemoglobin-oxygen affinity influence the pressure and amount of oxygen in the blood. The narrower [(A-a) DO2] can result in the better maintain S_pO_2 across a broad range of exercise levels. Zhuang et al. (22) reported that [(A-a) DO2] is lower in high altitude natives than acclimatized lowlanders.

Lower hemoglobin concentration in adult native Tibetans has been found previously (24;57-60). This is perhaps because Tibetans could better-maintain ventilation, or/and regulate the production of hemoglobin. The lower hemoglobin level of Tibetan children may be one of the aspects to explain why higher Wpeak was found in Tibetan children in this study. The increased hemoglobin-oxygen affinity can left-shift dissociation curve position and raise SpO_2 at a given arterial PO_2. The study by Wu et al. (24) and Garruto et al. (57) show that the difference in hemoglobin level continues into adulthood.

The amount of blood flow to the working muscles and other tissues depends on cardiac output. Cardiac Output (CO) is related to stroke volume (SV) as: CO = SV × heart rate (HR). It is suggested (1) that young Tibetan men have greater stroke volume than similarly-sized and aged healthy acclimatized newcomers at 3,700m due to their larger heart volumes. Well-maintained myocardial contractility and the low pulmonary arterial pressures result in the reduction in after-load in right heart may allow Tibetans to achieve a greater ascend in CO during exercise. One study suggested that the higher cardiac outputs in native highlanders compare to acclimatized newcomers due to higher heart rate (HR) and /or stroke volume (SV) (61). The higher heart rate at maximal exercise among Tibetan children shown in the present study may explain why they had higher W_{peak}.

Arterial venous oxygen difference reflects the **extraction of oxygen** and it can be influenced by the diffusion limitation of oxygen. Diffusion limitation of oxygen transportation in the lung is one of the factors influencing exercise capacity at high altitudes (62;63). It is shown that adult Tibetans have a higher diffusion capacity than the Chinese during exercise (62). Chen et al. (21) suggested that adult Tibetans have adapted more successfully than the Chinese to the high altitude environment, due to the greater capacity in their O_2 transport systems and greater exercise performance. Studies (64-67) have shown that an increased lung volume is accompanied by an increased pulmonary diffusing capacity. Sun et al. (19) reported that Tibetans have greater chest circumferences, which may indicate that they also have greater lung volume compare to the Chinese. In the present study, we support their finding that Tibetan subjects have significantly higher chest circumferences than the Chinese. Due to a possible greater lung volume among Tibetan children compared with Chinese, the Tibetan may have higher diffusion performance of oxygen in the lungs and, thus, better exercise capacity and better adaptation to high altitude.

Regarding **physical activity**, Tibetan boys presented higher exercise capacity even after the W_{peak} was adjusted for body weight while the difference between girls did not reach the level of statistical significance. This could possibly be explained by our finding that Tibetan boys are more active than Chinese boys in terms of doing exercise and playing games outside school while there are smaller differences among girls. This may also be supported by the finding that children who use bicycles to school presented significantly higher W_{peak} than those who did not use bicycles.

There is a tendency that the height of the children seems not to influence the W_{peak}. There are 383 Tibetan and 358 Chinese children who participated in the MWCE test. 57 Tibetan and 82 Chinese children lower than 130cm who could not attach the cycle pedal completely although they finished the test (Figure1). We found that the W_{peak} increases when the height increases in both Tibetans and Chinese. However, this relationship disappeared after adjusting for the confounding value weight.

2.2 Hemoglobin concentration

According to the World Health Organization (WHO) standard, the normal hemoglobin concentration is 12-14g/dl for children (68). Hurtado et al. (14) studied the increase in hemoglobin concentration in relation to altitude in the 1940s. Dallman et al. (69)

suggested that 4% increase in the concentration of hemoglobin per 1000 m elevation can be used for the adjustment to different altitudes of the reference populations defined at sea level. After adjusting, the normal value for the children living in Lhasa was 13.8-16.1g/dl. Wu et al. (24) reported the hemoglobin values for normal Tibetan boys (14.3 ±1.0), girls (14.0 ±1.1), Chinese boys (15.3 ±1.2) and girls (14.8 ±1.1) from age 5-15 at 3,813m (the average altitude of six pastoral and agricultural villages in the area near Habei at Qinghai-Tibetan plateau). This is fairly in accordance with our finding of 14.6 and 14.7 in Tibetan boys and girls, and it was 15.3 and 15.4 in Chinese boys and girls, respectively. Garruto et al. (57) measured haemoglobin concentration at 3,200 m and 3,800 m, and reported that the hemoglobin concentration is similar in Tibetan and Chinese children before puberty. The participants in the present study had not yet reached the puberty. However, most of the previous studies (24;57-60) indicated that hemoglobin concentration is higher in Chinese than in Tibetan residents of the plateau. It has been demonstrated that the findings of lower haemoglobin concentration in the Tibetan men, women, and children than in the Chinese population is due to the Tibetan population having acquired the genetic adaptation of an improved ventilatory responsiveness and/or blood oxygenation in hypoxia (24).

2.3 Arterial oxygen saturation

Studies (70-72) have demonstrated that arterial oxygen saturation decreases with increasing altitude and with exercise at high altitude. In the present study Tibetan children kept a higher level of SpO_2 than Chinese during the whole progress of the MWCE test although SpO_2 decreased from rest to maximal exercise for both ethnic groups. Huichao et al. (23) suggested that SpO_2 is utilised an indicator of acclimatization ability to high altitude in children. Thus, the higher SpO_2 at maximal exercise in the Tibetan children compared to the Chinese in the present study may also indicate that Chinese children are more at risk for development of CMS.

It has been shown (21) that the diffusing capacity could be a decisive factor for oxygen transportation during the maximal exercise at high altitude. Higher arterial oxygen saturation at a given level of oxygen uptake in the Tibetan compared to the Chinese adult subjects support that Tibetans have increased lung diffusing capacity (19). Moreover, diffusion limitation of oxygen transfer during exercise can result in arterial de-saturation at high altitude (65;73). Niermeyer et al. (74) reported that Tibetan infants have higher oxygen saturation from birth through four months of age compared to Chinese infants in Lhasa.

Arterial oxygen saturation can be influenced by alveolar ventilation, alveolar-arterial oxygen diffusion difference [(A-a)DO_2] and hemoglobin-oxygen affinity (1). Increased ventilation can decrease the oxygen-pressure gradient from the atmosphere to the alveoli and raise arterial oxygen tensions. There is a linear relationship between effective alveolar ventilatory sensitivity to hypoxia. For example, the loss of ventilatory acclimatization has been attributed to a loss of hypoxic ventilatory responsiveness. However, hypoxic ventilatory response is but one factor influencing resting ventilation.

Greater lung volumes are associated with increased surface area for better-maintained SpO2 during exercise. At a given workload, reduction in (A-a) DO2 permits high altitude natives versus acclimatized newcomers to better maintain arterial oxygen saturation. The increased hemoglobin-oxygen affinity can left-shift dissociation curve position and raise SpO_2 at a given arterial PO_2.

3 Conclusions

Tibetan children have higher peak workload, arterial oxygen saturation at maximal exercise and lower hemoglobin concentration as compared with Chinese. Tibetan boys are also more physical active than Chinese. These differences may indicate that Chinese are more at risk for CMS than Tibetan.

4 Research recommendations and future plans

In order to verify the hypothesis that Chinese children are more at risk for development of CMS, it is necessary to follow the population for many years and compare the incidence of CMS in the two groups of Tibetan and Chinese. Furthermore, it would have been of interest doing a follow-up to record changes in the main parameters under study (peak workload, arterial oxygen saturation at maximal exercise and hemoglobin concentration), and investigate if unfavourable values of these parameters predict CMS later in life.

A large number of Tibetans go for studying in inland China every year, and then return back to Tibet after several years. It would have been of interest to compare the parameters (peak workload, arterial oxygen saturation at maximal exercise and hemoglobin concentration) in a population of Tibetans who have finished their study of approximately 9 years in inland China, at sea level, and then moved back to Lhasa at 3,700 m, with control populations of Tibetan and Chinese adolescents who have studied all the time in Lhasa and Chinese who have lived all the time at sea level. The aim would be to investigate if the parameters become similar among the returning students as compared with Tibetans in Lhasa, and also to compare Chinese in Lhasa with Chinese adolescents in inland China at sea level.

From January 2007, the data from the present study and additional lung function data collected in the same population will be studied in more detail as a part of a PhD-thesis. More emphasize will also be put on investigation if selected factors (socio-economic and food habits) may explain differences in the main parameters under study between Tibetan and Chinese adolescents.

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Appendix I

Local conditions in Tibet

Geography

Covering a massive 1.22 million square kilometers, Qinghai-Tibet plateau is surrounded by the highest mountain ranges, the Himalaya to the south, the Karakoram to the west and the Kunlun to the north. **Tibet Autonomous Region (TAR)** is located at the main part of Qinghai-Tibet plateau in South-Western China. It borders with India, Nepal, Sikkim, Bhutan and Burma, and bounded by Kashmir on the west (1). With an average height of 4,000 meters above sea level, Tibet owns a group of giant mountains, Mt. Everest (8,848 m), and 4 mountains higher than 8,000 meters and 38 higher than 7,000 meters (2).

Lhasa, the capital city of the TAR, covers an area of 544 square kilometers and is "The Land of Gods" in Tibetan, sits on the north bank of River Lhasa, a tributary of the Yarlung Tsangbo River, at an altitude of 3,658 meters. Lhasa is the center of Tibet's political, economic, cultural and religious activities (3). Lhasa consists of one district and seven counties. The district comprises the urban area of Lhasa and is called Chengguan District. The seven counties are Lhünzhub, Damxung, Nyêmo, Qüxü, Doilungdêqên, Dagzê, and Maizhokunggar (4).

Demography

At present there are Tibetan, Chinese, Menpa, Luopa, Hui, Sherpa and a few Deng people living in Tibet. Tibetans are the main inhabitants on the plateau. According to the census conducted in 2000, there are 2,616,300 people in Tibet, with Tibetans totaling 2,411,100 (92.2%) and Han 155,300 (5.9%) (5). The total population of Lhasa is 474,499. Of this, 387,124 (81.6%) are Tibetans and 80,584 (17.0%) are Chinese (4).

The sex ratio of the total population in Tibet was lower than in the other provinces and regions. From 1951, the sex ratio of 94 or 95 women per 100 men remained the same for a long time. But after 1980 the sex ratio tended to increase slightly. The age composition in Tibet can be described as the Expansive Pattern with large number of people in the young ages: in 2000, 0.82 million were aged 0 - 14, about 31.2% of the total. The number of people aged 15 - 64 was 1.68 million, about 64.3%. The elderly 65 years old and above numbered 0.12 million, accounting for 4.5% of the total population (2).

Economy

The Tibetan economy has developed in recent years. In 2000, the GDP was 11.746 billion Chinese Yuan, the total gross output value of industry and farming, forestry, animal husbandry and fishery was 6.95 billion Yuan, and GDP per capita 4,559 Yuan. The total value of imports and exports in Tibet in 2000 reached 130.29 million US dollars. Government revenue was more than 6,898.05 million Yuan, and the output of grain was about 962,243 tons. At present, farming and animal husbandry are the major industries in Tibet. The gross output of farming, forestry, animal husbandry and fishery accounted for 73.67% of the total gross output value of industry and farming, forestry, animal husbandry and fishery in 2000. But productivity is very low, and manual farming and animal husbandry are still the primary pattern. Although in suburb a few machines are used for agricultural purposes, manpower and animal power are still applied in plowing the land. Therefore, agricultural production is neither high nor stable. In Tibet, the industry sector is quite small in size and diversity; it is characterized by extensive management at low efficiency (6).

School systems in Tibet

Primary level education in Tibet is the six-year *lobchung*. There are two types of *lobchung*: the *mangtsug* and *zhungtsug* schools. The *mangtsug* schools are set up by local people at the village level and receive no financial and facilitative support of any kind from the Chinese government. *Zhungtsug* schools are primary schools established by the Chinese government. They are found in the Tibetan cities and county headquarter towns and benefit an urban population which consists primarily of Chinese settlers. While a transfer from *mangtsug* to *zhungtsug School* is, theoretically, possible on the basis of a public examination, in reality it is said to rely heavily on personal contacts. Those students who complete *lobchung* schooling then have a chance to enter a lobdring - a six-year middle school. The lobdring is divided into junior middle school and senior middle school, each of three years duration. As with the case of the government-run *zhungtsug*, the lobdring are found in the large urban areas. Occasionally middle school branches can be found in townships but in some cases two or more counties have just one middle school between them (7).

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   URL:http://www.tibet-tour.com/abouttibet/geography.htm

2. Tibet introduction 2006

   URL: http://www.tibettrip.com/facts/intro.htm

3. Lhasa 2006

   URL:http://www.crystalinks.com/tibet.html

4. Lhasa

   URL: http://en.wikipedia.org/wiki/Lhasa

5. TAR general conditions 2006

   URL:http://www.tibetinfor.com.cn/dili/menu_dlgk_gk.htm

6. Tibet Economy

   URL:http://www.unescap.org/esid/psis/population/database/chinadata/tibet.htm

7. General background to the state of education in Tibet 1997

   URL: http://www.tibet.com/Humanrights/EduToday/chap2.html

Appendix II

Application for conducting field work

To whom it may concern,

I am a teacher from Tibet University Medical College. I am studying for the master degree of International Community Health in University of Oslo in Norway. I have returned for conducting my field work in Lhasa. The title of my project is “Exercise capacity among 9-10 year old children in Lhasa, Tibet”. The aim of the present study is to investigate possible differences between native Tibetan children and immigrant children with respect to selected factors which may be potential risk factors for later development of CMS, such as peak workload, hemoglobin concentration, and arterial oxygen saturation. The results of this study will be utilized for the purpose of increasing the awareness of CMS and its public health consequences, and to give useful information about further investigation, and provide important data for improving the life quality for the people who living in high altitudes, especially Tibetans.

Questionnaire, lung function measurement, maximal watt cycle ergometer (MWCE) test, oxygen saturation measurement will be applied in this study. Around 800 school children who were born between 1st of January and 31st of December in 1995 will be chosen. The subjects will be recruited from volunteers who can refuse to participate and withdraw from the study for any reason at any time without any consequences for themselves. Parents will on behalf of their children participate in this study. All information about the subjects will be handled confidentially.

This study will chose schools randomly from all the primary schools in Lhasa. Therefore, we sincerely expect to get permission form Education Office of TAR, each school and parents.

Bianba

Tibet University Medical College

Appendix III

Questionnaire (Childhood Health in Lhasa, Tibet)

No. □□□□□□□□

Date of answering the questionnaires: / /2005

Part A
Core questionnaire for demographic characteristics

1. Name of school
2. ______ Class _____ Grade

3. Are you a boy or girl? Boy□1 Girl □2
4. How old are you?_______ Years old

5. What ethnic group do you belong to?

Tibetan□1 Han Chinese □2 Han Moslem □3

Tibetan Moslem □4 Others__________ 5

6. How many brothers do you have?
Older brothers
Younger brothers

7. How many sisters do you have?
Older sisters
Younger sisters

8. How is your family financial condition (income) compare to other families?

Poor□1 quiet rich □2 very rich□3

9. Where were you born?

Lhasa□1 Shigatse□2 Nyingchi□3 Lhoka □4

Chamdo□5 Nagchu□6 Ngari□7 Others__________ □8

10. How long have you been in Lhasa? _________ years

11. What kind of place do you live in

In the middle of a city☐1 On the edge of a city☐2

In a town☐3 In a village☐4

12. What language do you speak mainly in your family?

Tibetan☐1 Chinese☐2 Tibetan and Chinese☐3 Others_____4

13. Do you know anything about ASTHMA?

Yes☐1 No☐2

If yes, how did you know it?
(Please tick all that apply)

	Yes☐1	No☐2
From your parents	☐	☐
From your sisters or brothers	☐	☐
From your friends	☐	☐
From your teachers	☐	☐
From books / newspapers	☐	☐
From radio / TV	☐	☐
Others		

Part B
Video questionnaire

14. Has your breathing <u>ever</u> been like this at any time in your life?

Yes☐1 No☐2

If yes, has this happened in the past 12 months? Yes☐1 No☐2

If yes, has this happened at least once a month? Yes☐1 No☐2

15. Has your breathing been like the boy's in the dark shirt following exercise at any time in your life?

Yes☐1 No☐2

If yes, has this happened in the past 12 months? Yes☐1 No☐2

If yes, has this happened at least once a month? Yes☐1 No☐2

16. Have you been woken at night like this at any time in your life?

Yes☐1 No☐2

If yes, has this happened in the past 12 months? Yes☐1 No☐2

If yes, has this happened at least once a month? Yes☐1 No☐2

17. Have you been woken at night like this at any time in your life?

Yes☐1 No☐2

If yes, has this happened in the past 12 months? Yes☐1 No☐2

If yes, has this happened at least once a month? Yes☐1 No☐2

18. Has your breathing <u>ever</u> been like this at any time in your life?

Yes☐1 No☐2

If yes, has this happened in the past 12 months? Yes☐1 No☐2

If yes, has this happened at least once a month? Yes☐1 No☐2

Part C
Core questionnaire for wheezing and asthma

19. Have you <u>ever</u> had wheezing or whistling in the chest at any time in the past?

Yes☐1 No☐2

If you have answered 'NO', please jump to question 25.

20. Have you had wheezing or whistling in the chest in the past 12 months?

Yes☐1 No☐2

If you have answered 'NO', please jump to question 25.

21. How many attacks of wheezing have you had in the past 12 months?

None☐1 1 to 3☐2 4 to 12☐3 More than 12☐4

22. In the past 12 months, how often, on average, has your sleep been disturbed due to wheezing?

Never woken with wheezing☐1 Less than one night per week☐2

One or more nights per week☐3

23. In the past 12 months, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breathes?

Yes☐1 No☐2

24. In the past 12 months, what have made your wheezing worse?
(Please tick all that apply)

	Yes☐1	No☐2
Weather	☐	☐
Pollen	☐	☐
Emotion	☐	☐
Fumes	☐	☐
Dust	☐	☐
Pets	☐	☐
Wool clothing	☐	☐

	Yes☐1	No☐2
Colds or 'flu'	☐	☐
Cigarette smoke	☐	☐
Food or drinks	☐	☐
Soaps, sprays or Detergents	☐	☐
Drug (Aspirin)	☐	☐
Others (please list below)		

25. Have you <u>ever</u> had asthma?

Yes☐1 No☐2

26. <u>In the past 12 months</u>, has your chest sounded wheezy during or after exercise?

Yes☐1 No☐2

27. <u>In the past 12 months</u>, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?

Yes☐1 No☐2

Part D

Core questionnaire for rhinitis

All questions are about problems which occur when you DO NOT have a cold or the 'flu'.

28. Have you <u>ever</u> had a problem with sneezing or a runny or blocked nose, when you DID NOT have a cold or the 'flu'?

Yes☐1 No☐2

If you have answered 'NO', please jump to question 33.

29. <u>In the past 12 months</u>, have you had a problem with sneezing or a runny or blocked nose when you DID NOT have a cold or the 'flu?

Yes☐1 No☐2

If you have answered 'NO', please jump to question 33.

30. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

Yes☐1 No☐2

31. In which of the past 12 months did this nose problem occur? (Please tick all that apply)

January☐1 February☐2 March☐3 April☐4 May☐5

June☐6 July☐7 August☐8 October☐9

September☐10 November☐11 December☐12

32. In the past 12 months, how much did this nose problem interfere with you daily activities?

Not at all☐1 A little☐2 A moderate amount☐3 A lot☐4

33. Have you ever had hay fever?

Yes☐1 No☐2

Part E

Core questionnaire for eczema

34. Have you ever had an itchy rash that was coming and going for at least six months?

Yes☐1 No☐2

If you have answered 'NO', please jump to question 39.

35. Have you had this itchy rash at any time in the past 12 months?

Yes☐1 No☐2

If you have answered 'NO', please jump to question 39.

36. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, around the neck, ears or eyes?

Yes☐1 No☐2

37. Has this rash cleared completely at any time during the past 12 months?

Yes☐1 No☐2

38. In the past 12 months, how often, on average, have you been kept awake at night by this itchy rash?

Never in the last 12 months☐1 Less than one night per week☐2

One or more nights per week☐3

39. Have you ever had eczema?

Yes☐1 No☐2

40. Have you ever had rhinitis?

Yes☐1 No☐2

Part F

Cough and phlegm

41. In the past 12 months, have you usually seemed congested in the chest or coughed up phlegm (mucus) with colds?

Yes☐1 No☐2

42. In the past 12 months, have you usually seemed congested in the chest or coughed up phlegm (mucus) when you did not have a cold?

Yes☐1 No☐2

If you have answered 'NO' to both of these questions, please jump over questions 43 and 44.

43. Do you seem congested in the chest or cough up phlegm (mucus) on most days (4 or more days a week) for as much as 3 months of the year?

Yes☐1 No☐2

If you have answered 'NO', please jump over question 44.

44. For how many years have this happened? _________ Years

Part G

Core questionnaire for your living (environment)

45. Which of the following pets do or did you keep inside your home?

(Please tick all that apply)

	Dog1	Cat2	Bird3	Rabbit4	Other animal5	No pets6
In the past	☐	☐	☐	☐	☐	☐
At present	☐	☐	☐	☐	☐	☐

46. Do or did you have at least once a week contact with any of the following animals outside your home? (Please tick all that apply)

	Dog1	Cat2	Farm animals (cow, sheep, goat, horse) 3	Other nimals 4
In the past	☐	☐	☐	☐
At present	☐	☐	☐	☐

47. Does your mother smoke?

	Yes1	No2
Never	☐	☐
Formerly	☐	☐
Currently	☐	☐

48. Does your father smoke?

	Yes1	No2
Never	☐	☐
Formerly	☐	☐
Currently	☐	☐

49. Has anyone smoked in the past or present inside your home?

Yes☐1 No☐2

If yes, how many cigarettes in total are smoked by all smokers per day in your home? (mother smokes and father smokes and other persons smoke)

	Less than 10 cigarettes1	10 to 20 cigarettes2	More than 20 cigarettes3
In the past	□	□	□
At present	□	□	□

50. How often, on average, do you eat or drink the following, nowadays?
(Please tick all that apply)

	Never□1	Less than once per week□2	1 to 2 times per week□3	3 to 6 times per week□4	Once per day or more often□5
Meat	□	□	□	□	□
Fish	□	□	□	□	□
Fresh fruits	□	□	□	□	□
Raw green vegetables	□	□	□	□	□
Legumes (peas, beans)	□	□	□	□	□
Flour	□	□	□	□	□
Rice	□	□	□	□	□
Butter	□	□	□	□	□
Fizzy drinks	□	□	□	□	□
Potatoes	□	□	□	□	□
Milk	□	□	□	□	□
Egg	□	□	□	□	□

	Never□1	Less than once per week□2	1 to 2 times per week□3	3 to 6 times per week□4	Once per day or more often□5
Cooked green vegetables	□	□	□	□	□
Burger	□	□	□	□	□
Fruit juice	□	□	□	□	□
Nuts	□	□	□	□	□
Hot Pot	□	□	□	□	□
Instant noodles	□	□	□	□	□
Dry beef	□	□	□	□	□
Dry lamb	□	□	□	□	□
Cheese	□	□	□	□	□
Tsamba	□	□	□	□	□
Tibetan barley beer	□	□	□	□	□

51. Please indicate how good your health is now:

Very good□1 Good□2 Quite good□3 Bad□4

52. Do you have any health problems?

Yes□1 No□2

If yes, please list here:

53. Are you usually feeling hungry when you go to bed at night?

Yes□1 No□2

If yes, how many times a week?

Once☐1 Twice☐2 Three times☐3

Four to five times☐4 Every night☐5

Part H

Core questionnaire for habitual physical activity

(Please tick only one)

54. How do you usually travel to school?

by car or motorcycle☐ 1 by bus☐2 by bicycle ☐3 by foot☐4

55. How do you usually travel home from school?

by car or motorcycle☐1 by bus☐2 by bicycle☐3 by foot☐2

56. How long does it usually take you to travel to school from your home?

less than 5 minutes☐1 5 to 15 minutes☐2 15 to 30 minutes☐3

30 minutes to 1 hour☐4 more than 1 hour☐5

57. What do you normally do at morning break?

sit down (talking, reading)☐1 stand, walk around☐2

run around playing games☐3

58. What do you normally do at lunch break (apart from eating lunch)?

sit down (talking, reading) ☐1 stand, walk around☐2

run around playing games☐3 go home for lunch ☐4

59. Which of these is most like you?

I don't exercise☐1 I exercise sometimes but not regularly☐2

I exercise regularly☐3

60. Which of these is most like you?

Either

I don’t exercise and I don’t intend to start☐1

I don’t exercise but I might start☐2

Or

I exercise regularly but have just started to do so☐3

I exercise regularly and have for over 6 months☐4

61. It’s up to me when I play games or sport

Definitely yes☐1 Maybe☐2 Definitely no☐3

62. I have more fun playing games and sports than doing other things

Definitely yes☐1 Maybe☐2 Definitely no☐3

63. Playing games and sports is the thing I like to do best

Definitely yes☐1 Maybe☐2 Definitely no☐3

64. I wish I could play more games and sports than I get a chance to

Definitely yes☐1 Maybe☐2 Definitely no☐3

65. At school there are playgrounds or fields where I can run around

Definitely yes☐1 Maybe☐2 Definitely no☐3

66. How often do you stay behind at school to take part in exercise

Hardly ever or never☐1 Once or twice a week☐2

Most days☐3 Every day☐4

67. How often do you play games outside after school

Hardly ever or never☐1 Once or twice a week☐2

Most days☐3 Every day☐4

If I went to do exercise most days....

68. It would get or keep me in shape

Definitely yes☐1 Maybe☐2 Definitely no☐3

69. It would make me better in sports

Definitely yes☐1 Maybe☐2 Definitely no☐3

70. It would be fun

Definitely yes☐1 Maybe☐2 Definitely no☐3

71. It would help me be healthy

Definitely yes☐1 Maybe☐2 Definitely no☐3

72. It would help me control my weight

Definitely yes☐1 Maybe☐2 Definitely no☐3

If I were to exercise most days...

73. It would give me energy

Definitely yes☐1 Maybe☐2 Definitely no☐3

74. It would help me make new friends

Definitely yes☐1 Maybe☐2 Definitely no☐3

75. It would help me be with my friends more

Definitely yes☐1 Maybe☐2 Definitely no☐3

76. It would help me look good to others

Definitely yes☐1 Maybe☐2 Definitely no☐3

Part I
Physical examination

77. Weight (Kg):_______ □□.□

78. Height (cm):_______ □□□.□

79. Seat Height (cm):_____ □□□.□

Circumference (cm)

80. Chest: ___ ①□□. □

②□□. □

81. Belly: ___ ①□□. □

②□□. □

Part J
Lung function test
(It will be registered automatically on computer)

PEF □. □□

FVC □. □□

FEF_1 □. □□

Part K Bicycle test

Time (min)	Workload (watt)	HR (beats/min)	SpO_2 (%)	
Rest	Lying down for 2-3min			
0	20 / 25			
3	40 / 50			
6	60 / 75			
9	80 / 100			
12	100 / 125			
15	120 / 150			Finished time (min)
18	140 / 175			

You have now finished. Thank you very much!!!

Appendix IV

W_{peak} for each school Table 3b is the comparison of the subjects from the first five schools, which include all the Tibetans and of Chinese children. The rest of schools (Table 3c to Table 3k) only include Chinese children.

Table 3b. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the first 5 schools.

		N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	1-Tibetan	201	107,3	13,3	0,94	0.000
	2-Han Chinese	125	101,4	14,2	1,27	
2-Girl	1-Tibetan	178	93,9	15,8	1,18	0.114
	2-Han Chinese	83	91,1	12,2	1,34	

Table 3c. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the first school.

			N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	H (cm)	1-Tibetan	22	133,0	4,8	1,03	,360
		2-Han Chinese	19	134,7	6,5	1,49	
	W (kg)	1-Tibetan	22	28,4	5,6	1,20	,707
		2-Han Chinese	19	27,7	5,8	1,34	
	W_{peak} (w)	1-Tibetan	22	110,2	13,3	2,84	,159
		2-Han Chinese	17	104,0	13,5	3,28	
2-Girl	H (cm)	1-Tibetan	19	134,5	7,9	1,82	,006
		2-Han Chinese	12	126,6	5,7	1,65	
	W (kg)	1-Tibetan	19	27,6	3,9	0,89	,000
		2-Han Chinese	12	22,1	2,2	0,65	
	W_{peak} (w)	1-Tibetan	16	100,5	13,9	3,47	,278
		2-Han Chinese	5	92,9	10,2	4,54	

Table 3d. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the second school.

			N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	H (cm)	1-Tibetan	49	134,4	5,6	,80	,179
		2-Han Chinese	23	132,4	6,3	1,32	
	W (kg)	1-Tibetan	49	29,3	5,1	,73	,189
		2-Han Chinese	23	27,6	4,7	,98	
	W_{peak} (w)	1-Tibetan	48	110,5	12,1	1,74	,053
		2-Han Chinese	21	104,0	14,1	3,09	
2-Girl	H (cm)	1-Tibetan	53	136,3	6,7	,92	,109
		2-Han Chinese	14	133,0	6,4	1,71	
	W (kg)	1-Tibetan	53	29,1	4,3	,59	,522
		2-Han Chinese	14	28,3	5,3	1,41	
	W_{peak} (w)	1-Tibetan	50	97,7	16,7	2,36	,684
		2-Han Chinese	13	95,6	11,6	3,21	

Table 3e. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the third school.

			N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	H (cm)	1-Tibetan	55	135,3	5,8	,78	
		2-Han Chinese	34	137,2	6,1	1,05	,149
	W (kg)	1-Tibetan	55	30,6	5,9	,80	
		2-Han Chinese	35	32,5	7,4	1,25	,185
	W_{peak} (w)	1-Tibetan	53	104,8	14,5	1,99	
		2-Han Chinese	34	103,7	15,7	2,70	,757
2-Girl	H (cm)	1-Tibetan	55	136,2	6,3	,85	,130
		2-Han Chinese	26	138,5	6,7	1,32	
	W (kg)	1-Tibetan	55	30,2	5,4	,73	,169
		2-Han Chinese	26	32,1	6,4	1,25	
	W_{peak} (w)	1-Tibetan	49	91,8	13,2	1,89	,415
		2-Han Chinese	25	94,6	15,9	3,19	

Table 3f. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the fourth school.

sex			N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	H (cm)	1-Tibetan	64	135,0	5,3	,66	,077
		2-Han Chinese	15	132,1	6,8	1,76	
	W (kg)	1-Tibetan	64	29,4	4,8	,60	,244
		2-Han Chinese	15	27,7	6,0	1,55	
	W_{peak} (w)	1-Tibetan	62	105,6	13,0	1,65	,181
		2-Han Chinese	13	99,8	17,9	4,97	
2-Girl	H (cm)	1-Tibetan	50	135,8	6,5	,92	,061
		2-Han Chinese	9	131,6	3,7	1,22	
	W (kg)	1-Tibetan	50	30,0	5,5	,78	,001
		2-Han Chinese	9	26,4	2,0	,68	
	W_{peak} (w)	1-Tibetan	48	91,2	16,0	2,30	,039
		2-Han Chinese	9	85,5	4,1	1,36	

Table 3g. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the fifth school.

			N	Mean	Std. Deviation	Std. Error Mean	P-value
1-Boy	H (cm)	1-Tibetan	17	136,0	5,1	1,24	,159
		2-Han Chinese	42	133,7	6,1	,93	
	W (kg)	1-Tibetan	17	30,3	4,8	1,17	,101
		2-Han Chinese	42	27,2	3,8	,58	
	W_{peak} (w)	1-Tibetan	16	108,5	12,7	3,17	,002
		2-Han Chinese	40	97,4	11,2	1,78	
2-Girl	H (cm)	1-Tibetan	17	134,9	6,2	1,50	,805
		2-Han Chinese	33	134,5	5,2	,91	
	W (kg)	1-Tibetan	17	27,7	4,8	1,16	,627
		2-Han Chinese	33	27,1	3,7	,64	
	W_{peak} (w)	1-Tibetan	15	90,1	18,6	4,81	,550
		2-Han Chinese	31	87,6	9,4	1,70	

Table 3h. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the sixth school.

			N	Mean	Std. Deviation	Std. Error Mean
1-Boy	H (cm)	1-Tibetan	0			
		2-Han Chinese	53	133,9	6,8	,93
	W (kg)	1-Tibetan	0			
		2-Han Chinese	53	26,8	3,5	,48
	W_{peak} (w)	1-Tibetan	0			
		2-Han Chinese	49	92,9	13,8	1,97
2-Girl	H (cm)	1-Tibetan	3	139,1	13,6	7,86
		2-Han Chinese	37	135,2	5,6	,918
	W (kg)	1-Tibetan	3	33,4	13,8	7,95
		2-Han Chinese	37	28,6	5,4	,88
	W_{peak} (w)	1-Tibetan	3	97,4	32,7	18,88
		2-Han Chinese	28	88,3	12,5	2,36

Table 3i. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the seventh school.

			N	Mean	Std. Deviation	Std. Error Mean
1-Boy	H (cm)	1-Tibetan	0			
		2-Han Chinese	11	132,8	5,2	1,56
	W (kg)	1-Tibetan	0			
		2-Han Chinese	11	27,0	4,4	1,34
	W_{peak} (w)	1-Tibetan	0			
		2-Han Chinese	11	93,2	12,3	3,72
2-Girl	H (cm)	1-Tibetan	0	132,1		
		2-Han Chinese	7	134,6	9,0	3,42
	W (kg)	1-Tibetan	0	29,1		
		2-Han Chinese	7	29,5	7,5	2,84
	W_{peak} (w)	1-Tibetan	0	63,3		
		2-Han Chinese	6	93,4	8,0	3,26

Table 3j. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the eighth school.

			N	Mean	Std. Deviation	Std. Error Mean
1-Boy	H (cm)	2-Han Chinese	15	129,0	5,7	1,47
	W (kg)	2-Han Chinese	15	25,5	3,3	,85
	W_{peak} (w)	2-Han Chinese	13	79,6	13,2	3,66
2-Girl	H (cm)	2-Han Chinese	13	130,2	7,1	1,95
	W (kg)	2-Han Chinese	13	25,3	2,5	,69
	W_{peak} (w)	2-Han Chinese	10	72,1	7,2	2,29

Table 3k. Mean W_{peak} among 9-10 year old Tibetan and Chinese children from MWCE test for the ninth school.

			N	Mean	Std. Deviation	Std. Error Mean
1-Boy	H (cm)	2-Han Chinese	22	130,7	4,8	1,02
	W (kg)	2-Han Chinese	22	26,0	2,5	,54
	W_{peak} (w)	2-Han Chinese	18	89,4	8,3	1,95
2-Girl	H (cm)	2-Han Chinese	18	130,2	4,4	1,03
	W (kg)	2-Han Chinese	18	25,0	2,2	,52
	W_{peak} (w)	2-Han Chinese	15	77,3	10,7	2,77